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THESIS.

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by

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RHYL.



THE ADMINISTRATION OF THYROID EXTRACT IN GENERAL
PRACTICE WITH SPECIAL REFERENCE TO A CASE OF
CARCINOMA.

Although Organotherapy has existed in some form from the most ancient times even amongst savages and primitive races of man, the method as at present practised is of recent origin.

Brown Sequard in 1889 suggested the employment of testicular juice in the treatment of the mental and physical deterioration of old age, experiments upon himself and others had yielded the most brilliant results, Brown Sequard's fluid or extract having a dynamogenic action beneficial in diseases attended with debility, especially in senile changes, pulmonary tuberculosis, leprosy, locomotor ataxia, anaemia etc.

Paul in 1892 advocated the hypodermic use of an extract of sheep's brains in conditions of neurasthenia; in this way extracts of almost every organ in the body have been used as cerebrin from the brain, medullin or myelin from the cord, renin from the kidneys, pepsin from the stomach, pancreatin from the pancreas, ovarin from the ovaries etc. But of all the extracts, that of the thyroid gland is still the most successfully employed and for certain conditions, such as myxoedema

and certain forms of goitre a specific, even more so than potassium iodide for syphilis or the salicylates for rheumatism.

There are many other conditions in which the gland has been more or less successfully employed, though perhaps without definite specific action, and one of the objects of this Thesis is to describe some cases in which it has been used with great success, and in which the modus operandi has been difficult to define.

Where the gland administered directly supplies the deficiency in the natural secretion, as in myxoedema the drug or animal extract may then be regarded as a true specific. In this connection I may mention that I have, in common with many others, seen and treated cases of myxoedema successfully by means of thyroid extract. These cases are by no means rare in general practice, though often overlooked, as the following brief notes of two cases will show.

Case I. A woman, aet 64, who consulted me about fourteen years ago, presenting the following classical symptoms of aggravated myxoedema; she had been an invalid for several years, but for how long the present symptoms had existed she could not tell. They came on gradually with general languor and weakness. When I saw her she had the most characteristic symptoms of solid oedema (which develops in the sub-cutaneous

tissues of the body, the severity of the symptoms depending upon the amount of injury which has been done to the secreting tissue of the gland, and not upon the nature of the process which has brought about the destruction of it, so that the same symptoms may follow fibrosis leading to atrophy conversion to goitre or removal by operation. Strictly speaking, myxoedema is a symptom or collection of symptoms of destruction of thyroid gland substance or tissue, just as ascites may be a symptom of cirrhosis of the liver. This general swelling or solid oedema of the whole body was more especially marked where the skin was loose, it was more scanty where the skin was firmly fixed to the structures that lay beneath it, for example, it was abundant on the back of the hand while little could be detected beneath the skin of the palm. The swelling in the subcutaneous tissue of the upper and lower eyelids was very marked the upper being wrinkled and the supra-orbital fossae filled up by the myxoedematous swelling. The skin below the lower eyelid was swollen and pendulous and looked translucent as if distended by fluid. As a result of the swelling of the upper eyelid it tended to droop and there was a difficulty in looking upward making the eyes look small, this difficulty was relieved by using the occipito-frontalis muscle by the contraction of which the eyebrows were often kept

elevated, this explained the transverse wrinkling of the forehead which is so commonly seen. The nose was thick and large, the cheeks were large, full, round and rather pendulous with occasionally a circumscribed pink flush, the lips were thick and everted, the mouth being widened, there was swelling under the chin of the subcutaneous tissues and the neck was very much thickened, with a general fulness in the supra-clavicular spaces; in fact, the swelling was general, preventing the patient from stooping or using her hands, the backs and fingers of which were swollen and also the feet. The abdomen was very much enlarged with all this myxoedematous swelling which was associated with great increase of the body weight (but, unfortunately for the patient, increased muscular and nervous weakness so that she could hardly walk or hold her head up having to rest it on the sternum.) The skin was dry and rough the superficial layers of the epidermis being shed as a fine powder. The hair was very thin, the front part of the scalp being bald, dry and scaly, the hair of the eyebrows and eyelashes being scanty. The patient always complained of feeling cold and felt cold to the touch, her temperature being always sub-normal a degree or two. Her intellect seemed rather dull, that is, she was slow in thinking or understanding any new project and she was very depressed; she complained of giddiness and

agoraphobia, walking near walls and avoiding open spaces. The gait was slow, leisurely and diffident, as Byrom Bramwell describes it "hippopotamus-like." The speech was slow, the voice hoarse and monotonous. The muscular weakness was so marked that she had great difficulty in getting about or holding up her head which rested on the sternum and when she sat down she could hardly get up again or lift her foot so that she could not mount a step without assistance. Anaemia was present as seen by the pale colour of the mucous membranes. The sounds and action of the heart were weak; the pulse was slow and of low tension; the digestion was poor; the bowels constipated; the urine was pale and of low specific gravity. There were a few crepitations at the base of the lungs, the chest expansion was poor and she suffered from attacks of bronchitis in the winter.

Treatment. During the first stage of the treatment our object was to remove the symptoms of the disease with as little risk and discomfort to the patient as possible; this stage is complete as soon as the patient is free from myxoedema. During the second stage we have, by preventing the return of the myxoedema, to keep the patient in the condition of good health which has already been attained by maintaining a sufficient supply of thyroid secretion.

As a result of this treatment the patient began to feel warmer, one of the earliest signs of improvement and a sure indication that a sufficient dose was being taken to produce the physiological action of the drug and that improvement in other directions would soon follow. There was a slight increase in the pulse rate but not out of proportion to the rise of temperature. The myxoedematous swelling diminished and finally disappeared, the strength returned, the patient was able to hold up her head and walk better, the mental depression passed off, her mind and body became more active and the general appearance was so much improved that her friends failed to recognise her on her return home to her farm in Ruabon. She lived for about twelve years from the time when she was first treated with the thyroid extract. Before coming to me she had been treated with baths and electricity without much benefit. As she was so very weak the dosage of thyroid extract was small and was increased very gradually, the patient being kept in bed until she became accustomed to the drug. We started with grain I, three times a day after meals. On the second day grains 6 in divided doses, continued this for two to three days watching results, fourth and fifth day grains 10 to 15 daily at the end of the week grains 5 three or four times a day. She stood this all right, I advised her to rest in bed for

half an hour after each dose, or to lie down, to avoid palpitation, in this way she could take up to 30 grains or more daily producing the maximum effect with the least possible discomfort and risk of overtaxing her heart.

Case II. This was one of Cretinism and was recognised without difficulty. The patient was a child whom I attended from birth. It was a consanguineous marriage the parents being Russian Jews. She was the third child having a brother and sister alive and well at the time of the birth of the patient; the boy, however, has since developed tubercular disease of the spine when he was seven years of age, this under treatment has progressed satisfactorily. Her sister, two years older than the patient, is quite healthy.

The patient is now 9 years of age and looks so well and normal in every way that it would be difficult without knowing the history to say that at one time she suffered from Cretinism. This happy result has been brought about by early treatment with thyroid extract, which has been kept up ever since.

Cretinism is endemic in the mountainous districts of Europe especially in the Swiss Alps, it is comparatively rare in this country, although examples may be met with in the hilly districts of Derbyshire,

Yorkshire and Somersetshire. Examples of this form of Cretinism may be met with in asylums. The case which I am about to describe was one of sporadic cretinism, the thyroid gland being absent. It developed in early infancy, the skin and subcutaneous tissues were thick, harsh and wrinkled and were of a yellowish chlorotic aspect, the eyelids puffy, the scalp was noticeable for its harsh scaly condition and the scanty growth of coarse hair upon it. The head was broad and flat being dolicocephalic, forehead small, face large, the bridge of the nose depressed. The lower limbs were stunted and the hands and feet flattened out, the abdomen large and pendulous with the navel protruding, the tongue being too big for the mouth and lolls from the open lips. The infant was dull and stupid, constipation was troublesome, there being no power to expel the faeces. The treatment consisted of extract of thyroid gland, grain I, two or three times a day, the dose being gradually increased until she showed the full physiological effect. The treatment has had to be continued, at the present time she takes two tablets, grains 5 each every week, any increase giving rise to glycosuria and incontinence of urine. She goes to school regularly, is of average size, and is fairly quick at her lessons but she is very sensitive if sharply spoken to or scolded by the teacher and loses control of her bladder.

. I have recorded these two cases as they seem to be fairly typical of the specific action of thyroid extract.

But the cases which I more especially desire to mention are those in which the drug or animal extract cannot be said to have definite specific action, in which, however, the results of this treatment have been satisfactory on the whole.

Case III. The most striking case was one of multiple carcinomata of the skin and subcutaneous tissue. I am aware that this is only a single instance, but the result was so gratifying that a record of the notes of the case may prove interesting. The patient, a widow, aet 61, gave the following history. In November 1899 she had a large pimple in the right axilla, and at the same time two nodules below the skin on the left side of the chest in the axillary line. The latter seem to have disappeared after the application of some ointment. The lump under the right axilla, however, continued to grow, until it attained the size of an ordinary marble, of a dark purple colour and at times this was very painful. At this period the general health remained good, apart from an occasional feeling of extreme cold associated with a greenish pallor of the face. The lump under the right axilla became so large and painful that in June 1900

she went to see Mr. Robert Jones of Liverpool, who advised immediate operation. This was done. In October of the same year she again consulted him for a growth under her left breast. She was urged to go again in a fortnight, to have this also removed, but, as in the meantime another growth occurred in the left side of the upper part of the abdomen, the patient was discouraged and did not go. During the months that followed several other fresh growths appeared, under the skin, two on the right side of the chest, one on the front of ~~the chest~~ the chest above the breast, two on the left side of the chest and last of all one under the right armpit. This made eight growths in all, varying in size from a walnut to a tangerine orange. By this time her general health was suffering severely. I saw her in June 1901 and found the growths as above described. The growth in the right axilla was the largest of all, fixed and painful, and was the size of a tennis ball; it prevented the arm from being brought to the side and had recurred at the site of the scar of the previous operation performed by Mr. Robert Jones (in June 1900.) The other growths were smaller about the size of filberts and walnuts. They were not painful but were tender on pressure and hard to the touch, and seemed characteristic of scirrhus cancer.

The larger growth (axillary) was, to all appearances

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not far from ulceration and breaking down. The patient appeared to be very anaemic, having a sallow greenish yellow colour, her pulse and respiration were quickened and her temperature varied from about 99° to 101°.

Sickness was frequent, the appetite was very poor, she was scarcely able to retain anything. The patient had lost three stone in weight.

As she had been operated on twelve months previously, with the unfortunate result mentioned, and owing to the dissemination of the growth and her feeble state of health, it was useless to suggest further operative interference, so I decided to try the effect of thyroid medication. Owing to her enfeebled state of health I administered tabloids of thyroid gland with extreme caution starting with grains 5 daily, gradually increasing the dose to grains 10, and finally, to grains 15 daily, adopting the same precautions as I did in Case I of myxoedema previously mentioned.

To my surprise the patient quickly showed signs of improvement, the palpitation, sickness and emaciation gradually disappeared, pari passu with the gradual disappearance of the growths. At the end of August 1901 the growths had entirely disappeared, the patient was practically well and had recovered her lost weight of three stone, and up to the present date is quite well, not having suffered in any way from them since.

I was so gratified with this result that I almost doubted the nature of these growths so I wrote to Mr. Robert Jones of Liverpool in December 1903 for his opinion of the growth he had removed in 1900. The following is his answer to my enquiry:-

"Dear Dr. Hughes Jones.

Thank you for your good wishes which I heartily reciprocate. I do not think I could look up the slide relating to Mrs. Jones but it was unquestionably a carcinoma, although I cannot quite recollect any of the pathological details. It was examined by a couple of men besides myself. Some time later there seemed to be a recurrence of the growth trouble and I recommended removal of the lump. However, she would not agree to that and I have often wondered what happened to it. This was some years ago, can you let me know in what spot the growth has recurred? Is it in the neighbourhood of the scar which you will find in the fold of the axilla or is it in the breast tissue?

Yours very sincerely,

Robert Jones."

My object in quoting this letter is to give an independent and authoritative opinion as to the nature of the growth, the corroborative nature of which, with the history shows it to be a case of carcinoma beyond dispute.

Case IV. Uterine Fibroid. Patient married, aet 37, two children, youngest aged 2 years; she began to have severe menorrhagia in 1897. She consulted me in 1898, about one year after the menorrhagia began. For two months she had been losing blood freely per vaginam every day with frequent floodings. She was markedly exsanguine from the profuse haemorrhage. There was an entire absence of symptoms except the haemorrhage. On vaginal examination the uterus was found to be enlarged to about a three months' pregnancy. Projecting from the posterior wall of the uterus into the pouch of Douglas was a firm rounded mass the size of a Jaffa orange. It appeared to bulge the cervical canal forwards, as well as to project on the serous surface. A sound passed into the uterus $4\frac{1}{2}$ inches. The cervix was patulous, admitting the finger, which detected the fibroid bulging forward in the cervical canal.

Palliative measures such as rest, douching, packing the uterus with gauze, curetting, the administration of ergot, orally and hypodermically were carefully tried with little or no influence upon the haemorrhage.

Thyroid extract grains 2 to 3 were tried three times a day and in increased doses, this was continued for a month. The haemorrhage gradually decreased and within a month of the beginning of the thyroid treatment it ceased altogether. The following three or four periods

were profuse but lasted only a few days. The patient then became pregnant. She had no unusual discomfort during the pregnancy and rapidly picked up her general strength. At the 8th month labour set in and she was delivered naturally of a still born child. There was no post partum haemorrhage. The fibroid involuted markedly during the puerperium. It should be noted that the patient was taking thyroid extract during the puerperal period and she has experienced no further discomfort or haemorrhage since.

Case V. The patient was a male, aet 21, who consulted me in 1906. He suffered from well marked scaly psoriasis on the extensor aspect of both arms, both legs also and the greater part of his back. He had suffered from the skin affection for some years and had been under various kinds of treatment. I thought it a good case to try the effect of thyroid extract so strongly recommended by some observers. Although he took it grains 5, three times a day for about a fortnight, there was very little improvement and it was discontinued.

Case VI. Psoriasis. Patient, male, aet 36, occupation bricklayer, who consulted me in 1907, was suffering from scaly psoriasis on the dorsal aspect of his hands, and extensor aspect of elbows and knees. The duration of t

the skin affection was some years. It was very much more limited than case V. He was put on thyroid extract, grains 5, three times a day and had Jeye's Fluid in bran baths. He improved markedly, the skin lesions all but disappearing within a few weeks, when he emigrated to America and remained there some months.

Case VII. Oedema. Patient female, aet 40. October 24. 1902 noticed that her left eyelid was irritable. At the time she was using chloride of lime for bleaching purposes, she happened to touch the skin at the corner of it and thought that she had burnt it. The lime may or may not have had anything to do with it but from that time it felt as if it had been scaled^d or burnt, it looked rather red but did not cause much trouble till Sunday October 27th when returning from church she felt it smarting badly, it continued until Wednesday when the left eyelid became swollen, Thursday it was worse, on Friday the right eyelid began to swell and burn and all night through the patient kept putting cold cloths on to relieve it without, however, much benefit. On November 3rd 1902 she had all the appearances of simple cutaneous erysipelas without, however, being ill in herself. The temperature and pulse being normal and the appetite good, the chief trouble was the great swelling, tension and

burning of the skin of the face and ears and part of the neck, so much that the eyelids were so enlarged and thickened that she could scarcely open them to see through. The lips and ears were twice their natural size the whole having that feeling of tension and stiffness which precedes erysipelas. With all these subjective and objective symptoms I expected a rise of temperature, or that the patient would complain of feeling at one time or another some chilliness, malaise, nausea, headache or pains in the limbs that usually accompany pyrexia, but she never once did during the whole of the six weeks the condition lasted, although she was taking diuretics, quinine, iron etc. Locally, ichthyol ointment 30, 40, and 50 per cent was applied constantly. Nothing seemed to have the least effect until I tried thyroid extract, grains 5, three times a day, gradually increased to grains 10, three times a day. She improved very quickly and was soon quite well. She had a recurrence of this trouble two years afterwards when a short course of thyroid extract soon put her right again.

Case VIII. Oedema. Patient, male aet 38, occupation printer, gets attacks of oedema of the face with swelling and tension of the skin over the forehead, eyes, cheeks and ears every few weeks in winter if

the weather is particularly cold, no constitutional symptoms, urine normal, appetite good. He was given thyroid tabloids, grains 5, three times a day, and got quite well. During convalescence there was a free desquamation of the skin.

Case IX. Retarded development in a Child aet 7, assuming the Mongolian type. So called on account of the resemblance to the Kalmuc or Tartar tribes of Asia. The characteristic features, first pointed out by Langdon Brown, namely, the oblique direction of the palpebral fissures, slanting upwards and outwards, drooping eyelids, the well marked epicanthic fold on the inner side, the squat round face with high coloured cheeks, smooth soft skin, good complexion, the usual squint and some nystagmus and hypermetropia corrected by ⁺x3 spherical lens were all present, the hands were normal, the finger tips being rounded with incurving of the little finger. She was very bright and lively in her manner, but could only use a few single words, and those not always distinct or sufficient to explain herself without pointing and gesticulating; the tongue was large and often protruding, and when she was spoken to she answered with a kind of snort. The head was rounded, the shortening being in the antero-posterior diameter, the occipital region was peculiarly

flattened so that the back of the head lost its rounded contour; the arch of the palate was very high and narrow; in addition to this her post nasal space was filled with adenoids which were removed, the result hardly coming up to one's expectation, one looked round to see if there was not anything else that could be given to improve the child. I therefore tried thyroid extract with the happy result that she walks and talks better and is brighter in every way, putting sentences together and speaking more coherently.

I am quite aware that there is, at first sight, a similarity between these cases and cretins, but, on close examination, the difference is obvious. The parchment like appearance of the skin which in parts is redundant so that there is a puffiness below the eyes and a puckering of the skin of the forehead, the head is dolicocephalic, the skin of the trunk is dry and rough, the hands are short and broad, the finger tips square, the disposition is slow, lethargic and dull, the tongue protruding and the bowels constipated. These differences, as well as the partial benefit that results from the thyroid extract in the Mongolian type is sufficient to distinguish the two conditions and, to my mind, justifies the giving of the thyroid extract to ameliorate, if not to quite cure, the

condition thereby affording some relief to the distressed parents and the patients themselves. How much of this improvement was due to the giving of the thyroid extract and how much to the removal of the adenoids, it is difficult to determine or to apportion correctly the true value of thyroid extract in this particular case of retarded development in a child of seven years.

PHYSIOLOGY AND CHEMISTRY.

In order to understand how thyroid gland acts it is necessary to consider what is known of its function. It supplies an internal secretion which escapes by way of the lymphatics into the blood stream by which it is distributed to all parts of the body to which it is so necessary.

The thyroid is a ductless gland and the colloid substance which fills its acini is its internal secretion or contains it.

The colloid is formed from the granules which can be seen in the cells of the acinus; these granules discharge themselves into the lumen of the acinus, where the colloid collects until a separation of the cells is produced by pressure and the colloid is emptied into the lymphatic spaces. From these spaces

the lymphatic vessels convey the secretion into the blood stream by the thoracic duct, etc. According to some observers the colloid is directly absorbed also by the capillary blood vessels. Chemical examination of the gland shows that it contains two proteids, a nucleo-albumen and the colloid substance. This latter substance is a compound proteid containing iodine, the percentage varying, but forming about 3 per cent of the dried gland. The colloid is not a nucleo-proteid as no nuclein is yielded by gastric digestion. When the colloid is subjected to digestion, only those substances which contain iodine possess active properties. The active substance, called iodothyrim, produces the same effect on the metabolism of the body as the gland substance itself. It is a brown amorphous substance, almost insoluble in water, but readily soluble in weak alkalis.. It contains 0.56 per cent of phosphorus and about 9.3 per cent of iodine and gives no proteid re-action. It is not probably a derivative of nuclein but its composition is not yet exactly known.

Whether this substance is really the important proximate principle in thyroid extracts and by inference in the normal internal secretion of the organ, must still be left to the future. For, though Roos and Baumann state that it acts in every way like

thyroid extracts, Gottlieb has been unable to confirm the statement, though possibly, as Auerbach suggests, this is to be attributed to his having used preparations very poor in iodine. Weak points in the theory appear to be the absence of the substance in the thyroids of children, and in some animals like dogs unless they are put on a particular diet (dog biscuits). Small quantities of iodine are found also in the thymus.

Drechsel has confirmed the existence both of Baumann's iodothyrim and of Fraenkel's thyreo-antitoxin and had further separated out a second crystalline base. Hutchinson, however, finds that the proteid-free extracts which contain these bases are physiologically inactive. He finds that the activity is connected with the iodine-containing colloid substance. He distinguishes between the colloid of the acini and the nucleo-proteid of the epithelium lining them. The former is the active constituent, and is by gastric digestion decomposed into two parts. One part is proteid; it contains a little iodine, and has feeble physiological powers. The other part is not proteid and not nuclein. It is more active and contains the greater part of the iodine and all the phosphorus of the original colloid.

PHARMACOLOGY.

Action of Thyroid Extract. The thyroid extracts and iodothyrim seem to be devoid of effect in many normal animals and patients, unless when given in enormous quantities. In others they cause unpleasant symptoms which occur more especially in cases of myxoedema and goitre. These symptoms are partly subjective and indefinite, such as headache, wandering pains or general weakness, while others are evidently due to circulatory changes and consist of a feeling of fulness and congestion of the head, palpitation of the heart and acceleration sometimes weakness of the pulse. Tremors in the arms and legs point to changes in the central nervous system, while loss of appetite and diarrhoea indicate that the alimentary canal is not exempt from its influence. Perspiration is often complained of especially in myxoedema and a rise of temperature also occurs not infrequently. In normal animals iodo-thyrim injected intravenously in large quantities generally accelerates the heart and lowers the blood pressure. When given by the mouth for several days it produces the same effect, probably due to stimulation of the accelerator centres: according to other observers it is due to direct

action on the heart. Loss of flesh and thirst have been observed even when the appetite is good and sufficient food and water supplied to the patient. The urine is universally increased in amount. A number of observers have found that the continued administration of thyroid preparations in large amounts leads to diarrhoea, muscular weakness especially in the hind extremities, emaciation, gastro enteritis, nephritis and fatty degeneration of various organs. In other instances no such symptoms have been elicited, the animals remaining perfectly normal after prolonged treatment. Some of the symptoms induced in man by an overdose of thyroid extract resemble those seen in exophthalmic goitre which had been observed in monkeys to which large amounts have been given. As may be gathered from the above great discrepancies occur in the accounts of the effects of thyroid extract in normal animals and men, however, the acceleration of the heart and the fall in weight seem to be the most common result. The effects of thyroid extract on metabolism have been repeatedly examined with uniform results and one of the most striking features in many animals and in many individuals is the rapid loss of weight, which often amounts to several pounds per week. Another is the increase in the amount of nitrogen in the urine which

occurs both in goitre and myxoedema and very often in an apparently normal person.

More nitrogen is being excreted in the urine than is frequently taken in the food, that is to say, thyroid extract leads to the destruction of the proteids of the tissues. If more nitrogenous food be taken, however, this may be arrested, in fact, if large quantities of meat be taken less nitrogen may be excreted than is taken in the food. So that, although the patient may be losing weight, he may actually be increasing in nitrogenous tissue. If, on the other hand, a patient has been put into nitrogenous equilibrium and then, under thyroid, begins to excrete more nitrogen than he ingests, this excessive tissue waste is not stayed by an increased quantity of carbohydrates and fat; that is, the carbo-hydrates and fats cannot replace nitrogenous food to the same extent as in normal individuals. Thyroid extract has thus a specific effect in increasing the waste products of the body. But this increased waste of the proteids only accounts for one-sixth of the loss of weight, the other five-sixths being evidently due to the increased rapid oxidation of fats and the removal of fluid from the body.

Schondorff states that in nitrogenous equilibrium the oxidation of the fats is increased before the

proteids of the body are attacked, but, when the fat destruction has reached a certain point, the proteid waste is also increased. The early augmentation of the nitrogen of the urine does not indicate an acceleration of the proteid metabolism but is due to the removal of urea and other products which have been formed in the tissues before the administration of the remedy but which are now excreted through the increased activity of the drugs.

The most rapid oxidation is further evidenced by the increased amount of oxygen absorbed and of CO₂ exhaled by the lungs.

The removal of fluid from the body, perhaps the most potent factor in reducing the weight in these cases, is shown by diuresis which occurs in myxoedema especially, but also in obesity,

This has been ascribed to some specific action on the kidney, or to the changes in the circulation, but may perhaps be due to the increased excretion of urea and other urinary substances.

That the kidney is acted upon in some cases is shown by the occasional appearance of albumen in the urine of patients treated with thyroid preparations.

The phosphates are increased in the same ration as the nitrogen and the increase is obviously due to the same cause, augmented proteid waste.

In some cases sugar has been found in the urine after thyroid treatment and in a considerable percentage of persons it seems to cause a tendency to glycosuria as is shown by the appearance of sugar in the urine after the injection of large quantities of sugar which would normally be oxidised with tissues. The uric acid excretion is not affected.

After Iodo-thyrin has been administered, iodine is found in the urine in the form of iodide, so that iodothyron is evidently decomposed at any rate in part in the body. The rest of the iodine is taken up by the thyroid gland and it would appear probable that it enters into it in the form of iodothyron and that no preliminary decomposition occurs here.

In regard to thyroid medication individuals vary considerably, for many are scarcely affected by it in any way and this is particularly true of children, while others lose weight rapidly and under large doses show symptoms of thyroidism. These seem to be more easily elicited in goitre and myxoedema than in ordinary cases, on the other hand in some cases of Grave's disease the symptoms are generally aggravated by it. Many authorities believe that Grave's disease is due to an over production of iodothyron not proved though there is considerable support and theory.

The fact that " thyroidism " occurs more frequently

in myxoedematous than in normal persons seems difficult of explanation but it has been suggested that the symptoms are not due to the iodothyron itself but to the products of its action. It may be supposed that in myxoedema a large amount of iodine substance accumulates in the tissues because the iodothyron is not present in sufficient quantity to decompose it, and that, when thyroid treatment is commenced, the body is flooded with products of decomposition and these give rise to the symptoms. In normal persons on the other hand there is no such accumulation and iodothyron therefore induces no symptoms until it is given in such quantity as to induce intoxication itself.

Therapeutic uses of thyroid gland extract is not a dangerous remedy except in certain cases. In myxoedema it should be used with care especially if the heart is seriously affected and the cardiac muscle may be unable to meet the requirements of the accelerated rhythm. Several serious cases and two fatal ones have been recorded in these conditions,

Iodothyron is a useful substitute for the normal gland secretion in cases where the latter is wanting or deficient, for example, myxoedema etc. This has to be continued for a long time or perhaps throughout life or the patient will relapse into her former

condition.

The decrease in weight in thyroid medication suggested its use in obesity and it has been successfully used in a number of cases especially when accompanied by proper dietetic treatment. In many instances it has little or no effect and the encouraging initial action is seldom maintained.

It should be remembered that thyroid treatment is liable to cause cardiac failure and that fatty degeneration of the heart is a common accompaniment of obesity. The treatment moreover has to be kept up for a long period. The results are so problematical and the dangers so great that there is considerable doubt concerning the benefit to be derived from this form of treatment. Some authorities such as Yorke Davis, Magnus-Levy and Ebstein regard thyroid medication in obesity as unjustifiable.

SUMMARY.

Thyroid extract is an infalliable remedy for myxoedema and Cretinism as shown in Case I and Case II and is therefore a true specific supplying the deficient normal secretion due to absence of the gland.

Its curative effect in these cases can be explained by its pharmacological action, the thyroid secretion stimulates and brings into renewed activity all the most important functions of the organs of the body, for example, the urine is greatly increased in quantity, the specific gravity being raised indicating more excretion of solids and this is explained by a dehydration of fats leading to an increase of water and salts in the blood.

The mental hebetude which was so marked a feature gradually passed off, her speech lost that slow hesitating deliberate character and became more free and natural at the same time the feeling of languor and inability to make any exertion without great effort gave way to a condition of lively interest in herself and surroundings. The daily duties which had been irksome and difficult of accomplishment even eating walking or dressing herself being a trouble to her, the memory once more became active so that the same difficulty was not experienced in recalling names and recent events, all this showed increased mental activity due to more active cerebation after the administration of the thyroid extract.

The body temperature was raised about two degrees owing to the increased oxidation giving her a degree of comfort and freedom from the feeling of chilliness

which had been such a troublesome symptom..

The effect upon the cutaneous system was very marked, the skin became soft and moist, the swellings in different parts of the body disappeared the skin lying in folds especially round the eyes and other parts where there had been great swelling. The tension being relieved, muscular movements became easier, she was able to lace her boots and to pick things up. As a result of this swelling passing off, her whole personal appearance changed, and became more natural. The hair grew on her head and the eyebrows and eyelashes re-appeared. This evidently shows the particular action of thyroid gland upon skin and epithelial tissues, the lymph circulation is increased, the thyroid secretion circulating in it probably leads to increased glandular secretion which is the result of increased metabolism as evidenced by the rapid loss of weight. The actual weight was not ascertained, but, judging by appearances, it must have been several stones when she left off the treatment in about two months' time.

The cases of cretinism I need not go into in detail the above remarks applying in the main to this. It is necessary however to mention, the greater susceptibility to the action of the thyroid extract and the accidental condition of glycosuria in the cretin. When a little

over the sufficient dose was taken this occurred during the later years of treatment. It is believed by Lorand and others to be due to the colloid matter of the thyroid gland being broken down and yielding glucose to the blood the excess being ultimately destroyed by the internal secretion of the pancreas. Incontinence was another difficulty which came on about this time and may have been due to the extra stimulation by the thyroid extract increasing the sensitiveness of the micturating centres which brought on incontinence. This was always worse during excitement or in school when she was reprimanded by her teachers, she was not troubled at night. The glycosuria passed off when the drug was left off or diminished in quantity. Fortunately early diagnosis was made before much damage had been done to the cells of the cerebral cortex.

THYROID EXTRACT IN CARCINOMA.

After reviewing the results of thyroid administration obtained by other observers much less after the result in the case I have just recorded any impartial observer must conclude that thyroid organotherapy cannot, in any sense, supersede the well recognised methods of

surgical procedure in operable carcinoma. The free removal of the growth during the operable stage must stand as the soundest and most hopeful measure of curative treatment. When, however, complete radical treatment is out of the question and when operative measures are refused by the patient, even in the operable stage, thyroid administration offers some hope of checking the rapidity of the growth, favouring spontaneous cure and possibly achieving the slow but absolute disappearance of the growth.

There are now on record a number of well authenticated cases of carcinoma in addition to my own case which have to all appearance entirely disappeared under the administration of thyroid extract. Their numbers are not great but they are sufficiently striking to lead me to conclude that the association of thyroid administration with the cure is more than a mere coincidence.

A still larger number of cases of carcinoma have been recorded where thyroid administration was followed by disappearance of secondary nodules, increase of weight, loss of pain and other signs of marked local and general improvement but not complete cure of the growth. In these cases treated by thyroid there appeared to be established a negative phase of growth in the neoplasm during which the nodules or

mass ceased to grow or retrogressed and in many cases underwent a spontaneous cure.

Many of the cases which were thus favourably influenced by organotherapy had double oophorectomy performed previous to the administration of this animal extract. Double oophorectomy found its great advocate in Beatson and was applied particularly to women below the menopause. Beatson¹ supported by other observers such as Hermann, Stiles, Chicken, McAdam Eccles and others advocated Oophorectomy with subsequent thyroid administration as a justifiable procedure to recommend to patients short of the climacteric who were suffering from inoperable carcinoma, particularly of the breast.

It was found by almost all observers that after the menopause there was little or no advantage in performing double oophorectomy simply because the ovaries had ceased their active sexual life and ceased to influence the metabolism and more particularly the proliferating properties of cells of the body.

The case I have just recorded is an example of carcinoma arising after the menopause and was treated after recurrence of the growth following operation by thyroid treatment alone. All the observers such as Beatson, Hermann and Stanley Boyd who have employed oophorectomy combined with thyroid extract are agreed

that the results are much better in the combined treatment than where oophorectomy is employed alone.

In Mr. Stanley Boyd's series of 40 collected cases of cancer of the breast treated by oophorectomy or by oophorectomy and thyroid extract combined the value of thyroid extract was strikingly exhibited in the 17 cases of this series which were favourably influenced by oophorectomy in at least 12 of them this was combined with thyroid administration, whereas in the remaining 23 cases which appeared to derive little benefit from oophorectomy thyroid extract was given in only five or possibly six of the cases.

This would appear to show that the thyroid administration had an important beneficial influence upon the cancerous growth. It must at once be admitted that thyroid extract has given the best results in cancer of the breast.

In cancer of the viscera, such as intestine and uterus, it has so far given few, if any, results comparable to its successes in the inoperable cancers of the mammary gland. Nearly all observers are agreed that in cases where visceral metastases already exist thyroid extract, combined or not with oophorectomy, has little or no influence upon the disease. The kind of case most suitable for thyroid treatment as urged by Beatson and others is where secondary growths occur

only in the skin and lymphatic glands but where visceral growths are absent.

Before attempting to explain something of the modus operandi of thyroid administration in carcinoma, I would like to refer to a number of cases of cancer which have apparently disappeared under the treatment of oophorectomy and thyroid treatment, references to which will be appended.

1. The Author's case. Cancer of axilla, recurrence after operation with secondary nodules, duration of growth $2\frac{1}{2}$ years, freedom from growth, after thyroid treatment alone for 8 years.
2. Stanley Boyd's case. ⁽²⁾ Cancer of breast, secondary nodules, lymphatic glands, duration of disease 8 years, freedom from disease $3\frac{1}{2}$ years after oophorectomy.
3. Hermann's case. ⁽³⁾ Cancer of breast, recurrent secondary nodules, after operation, axillary glands, duration of disease 9 years, freedom from disease after oophorectomy and thyroid treatment $3\frac{1}{2}$ years.
4. Cheyne's case. ⁽⁴⁾ Cancer of breast, removed by operation, recurrence in axilla, duration of disease 5 years, oophorectomy and thyroid treatment, apparently free from glands 12 months after.

- (5)
 5. Waterhouse's case. Cancer of breast, breast removed, recurrence in axillary and supra-clavicular glands, duration of disease $3\frac{1}{4}$ years. Oophorectomy and thyroid administration, disappearance of glands in 4 months and remains apparently well for 8 months.
- (6)
 6. Beatson's case. Cancer of breast, recurrence in glands, duration of disease 5 years, oophorectomy and thyroid administration, freedom from disease 2 years.
- (7)
 7. & 8. Cheyne's two cases of cancer of the thyroid gland.

Writing to me on April 20th 1909, Sir William Watson Cheyne says:- " I have not written anything on the matter you speak of, but I did mention to Bashford two cases which, I feel sure, were malignant disease of the thyroid which got well after administration of thyroid extract."

It will thus be seen that in all these recorded cases of apparent cure of cancer thyroid extract was administered in all except Stanley Boyd's case. In the three of them, the author's case and in Cheyne's two cases on cancer of the thyroid gland, thyroid organotherapy was used alone. These facts, together with the still larger number of cases in which the

growth was undoubtedly favourably modified and partially arrested by oophorectomy and thyroid administration, compel one to the conclusion that in this form of organotherapy we have a valuable means of treatment of cancer. In no sense can it be regarded as specific but that it favourably influences the cancerous growth and enables the tissues to bring about a partial, and in some cases a complete, spontaneous cure is highly probable. It must of course be understood that the author does not in any sense seek to supplant the well recognised methods of radical removal by operation where this is possible. It would appear to be applicable to cases of inoperable carcinoma or recurrent cases of a limited extent.

I should further be prepared to advise thyroid administration as an adjunct to operative measures in operable carcinoma hoping by such administration to prevent recurrence and to enable the tissues to deal with minute foci of cancer which have escaped radical removal by surgical treatment.

The modus operandi of thyroid organotherapy in carcinoma is a matter of pure speculation. Physiologists, however, have evolved so much of the action of thyroid secretion upon body metabolism that it is possible to suggest a plausible theory as to how this

internal secretion or the administration of its animal extract by the mouth does influence the cellular growth of malignant disease.

Before attempting this, I would like to refer to some of the facts concerning the life history of cancer cells and their spontaneous disappearance which have been brought to our notice by Bashford, Handley, Bonney and others.

There is now on record abundant clinical and experimental proof of the spontaneous cure of cancer. The clinical evidence is forthcoming in the authentic cases of complete spontaneous cure of mammary cancer published by Pearce Gould⁽⁸⁾ and Mackay⁽⁹⁾ as well as the cases previously mentioned. Further support is given of this in the healing of cancerous ulcers as shown by Pearce Gould in 1900, the occasional healing of fractures of bone due to cancerous growths, the disappearance of spinal metastases, as shown by Osler,⁽¹⁰⁾ and the shrinkage of atrophic scirrhus. Careful observation has been made upon secondary nodules of the skin and it has now been proved beyond all doubt that many of these entirely disappear.

(II)

On the experimental side, Bashford and Murray, at the Imperial Cancer Research Laboratories, have demonstrated clearly that spontaneous disappearance of cancer masses is by no means a rare occurrence in

mice after artificial propagation. They have observed tumours at first manifesting rapid growth followed by cessation of growth and frequently by complete absorption.

(12)
Handley, in a recent paper dealing with spontaneous cure of cancer in the human subject, enunciates the following law concerning cancerous growth:-

" Every aggregation of carcinoma cells has a definite life-cycle and, after increasing in size for a varying period, and at a varying rate, tends spontaneously to undergo degenerative and fibrotic changes. These changes extend from the centre of the mass centrifugally to its periphery, lead to its shrinkage and terminate in the replacement of the aggregation of cancer cells by a fibrous scar."

In other words, the natural history of a cancer is one of centrifugal growth, followed by centrifugal death.

This law, of course, is difficult of proof clinically, because, in the majority of cases, death of the patient takes place before the full life-cycle of the cancer mass is complete. What is quite certain, however, is that the spontaneous cure of cancer is a local process and not a constitutional one. In this respect it resembles tubercle. In cancer, the natural cure beginning in the centre of the growth, rarely overtakes the centrifugal spread of the growth at the margin,

although, in certain rare cases, the central degeneration and fibrosis is so rapid that it strangles the growing edge and leaves but a scar behind.

Bashford and Murray, in the experimental inoculation of cancer in mice, have made observations upon the life history of cancer masses which are very much in accord with those of clinical observers. They have demonstrated remarkable fluctuations in the rate of growth of cancer masses, sudden exacerbations of rapid growth being followed by sudden cessations of growth to which they have given the names of positive and negative phase. These fluctuations are probably due to one of two causes, namely, either to variation of suitability of the soil in which the cancer cells are growing, or, to variations inherent within the cancer cells.

Both Handley and Bashford, the one working clinically and the other experimentally, have proved that cancer cells are obligatory parasites and that they are dependent for their life upon the connective tissue cells in which they lie.

The rate of spread of the cancer is dependent, partly upon the suitability of the soil or connective tissue just external to its advancing margin, and partly upon the inherent properties of cell proliferation within the cancer cells.

(13)

Victor Bonney in his Hunterian Lecture, established a new important fact bearing upon the origin of cancer. It was that a local increase in the cellularity of the sub-epithelial connective tissues accompanied also by a destruction of the elastic tissue, invariably precedes the appearance of carcinoma. This increased cellularity is due to a precedent chronic inflammation. If the chronic inflammation has progressed farther and has reached the stage of fibrosis and diminished cellularity he finds that there is little risk of a carcinoma originating in the fibrosed area. The same increased cellularity of the connective tissue is seen at the margin of a growing cancer. It is therefore obvious, that, as a cancer cell is but a parasite on the connective tissue cell, any abnormal aggregation of the connective tissue cells will only act as a body of hosts or caterers to the cancer cells and therefore favour their growth.

Therefore, if, by any means, the proliferating highly cellular connective tissue at the margin of the cancer mass can be converted into a fibrotic area, the rapidity of the cancer invasion is arrested and a negative phase of growth is obtained.

The above are a few of the facts known to us which govern the growth of cancerous masses.. Handley has shown that fibrosis around cancerous masses does take

place, not only in the connective tissue around the growth, but also in the lymphatic vessels leading away from it, and, in this way, the cancerous invasion is arrested.

Is there anything in these facts which can throw any light upon the probable action of thyroid extract in favouring the spontaneous cure of cancer in the human subject?

Physiologists have shown that thyroid secretion has a powerful action upon proteid katabolism as shown by increased nitrogenous excretion and loss of body weight. They have further shown that it lowers the blood pressure causing increased circulation of lymph. This increased lymph circulation renders the blood more watery and causes dehydration of the tissues.

These two physiological actions appear to me to offer some explanation of the beneficial action of thyroid extract in certain cases of cancer. The increased proteid katabolism might act in two ways. In the first place, it would shorten the life history of the cancer cells by stimulating katabolic processes in them and thereby favour degenerative processes and fibrosis of the central mass of the growth. In the second place, its influence upon the connective tissue immediately adjacent to the cancer focus is, probably, still more important. By its stimulation of proteid

metabolism within the connective tissue cells, its acceleration of lymph flow and dehydration of the tissue, it would modify the increased cellularity of the sub-cancerous zone of connective tissue which, according to Bönney, is so favourable to cancerous invasion by converting it into fibrotic connective tissue and thereby arrest the centrifugal growth of the growing edge. By this dual action of quickened life-cycle of the cancer cells and fibrosis of the connective tissue around a negative phase of the growth is obtained.

So much stress was laid by Handley and others upon the fortification of the soil, as represented by the connective tissue upon which the parasitic cancer cells depend for their nourishment, that they strongly advised that every attention should be paid to the general health of the individual, for example, they advocate open-air treatment and forced feeding as in tuberculosis, in order to give the tissues every chance of overcoming the cancer nodules.

In some such manner, the administration of thyroid extract may favourably influence carcinoma and help to bring about spontaneous cure.

Case IV. Uterine fibroid. Its action in these cases is more obscure, it probably acts by affecting the lymph stream and cell growth. Several cases have been recorded, mostly about the time of the menopause.

Watson Cheyne gives an instance in the B.M.J. Oct 20. 1900 patient had several operations for cancer of breast and was losing blood freely from a large fibroid. Oophorectomy and incomplete removal of recurrence May 1899. October 1899 (five months) reported free from obvious cancer, thyroid colloid tabloids steadily given, one tabloid three times a day. July 1900 (14 months) in better health than for some time past. Recently had a large gland above clavicle, fibroid almost gone.

Other cases might be quoted but the above is sufficient to illustrate its action.

Case V. and VI. were ordinary case of psoriasis with no specific history as far as one could make out. One was considerably relieved and upon the other there was no effect again illustrating its varying effect upon different individuals, although from the known particular action of thyroid products in cutaneous affections the same results might have been expected. Byrom Bramwell thought that thyroid extract might be useful in the following conditions, (Brit. Med. Assoc. 1893):- Psoriasis, Ichthyosis, Lupus vulgaris, acute and chronic Eczema and various forms of Alopecia. In these conditions it may act on special nerves enervating the skin, increasing epithelial proliferation, and stimulating action of sweat glands. Some think it

may be due to the iodine it contains, iodine being found in the urine in the form of iodide shewing that it is evidently decomposed at any rate in part in the body.

Cases VII and VIII were ones of solid oedema without any constitutional symptoms; the face and parts of the head and neck being principally affected, this might be explained by some irritant circulating in the lymph stream leading to blocking and some stasis in certain areas.

The first case No. VII is very instructive and illustrates the effect of thyroid gland upon what is known of lymphatic circulation, increasing its activity probably in the glands and vessels, and as a result the swelling and induration disappeared, the skin became moist and soft, as it does in cases of myxoedema and cretinism treated with thyroid extract. This view is suggested by the state of the skin lymphatic and sweat glands in exophthalmic goitre where almost invariably the skin is moist and warm, the patient seems specially tolerant of cold, anything in these cases that increases the action of the skin such as thyroid extract only aggravates the trouble there being already a hyper activity of the glands leading to an excess of thyroid products in the circulation.

In case VII the condition returned in about two years' time, in the meantime the patient had removed to the north of England and requested that some more tablets might be sent to her as they had done her so much good in the previous attack. This is merely mentioned to show that nothing else would relieve this patient's condition except thyroid extract, she never to my knowledge had suffered previously from this condition.

Case VIII was interesting as showing the beneficial effect of thyroid in conditions where cold was the exciting cause, of the swelling of the face which only came on during severe weather, the patient being particularly free from it during the summer.

Case IX was one of the Mongolian type of retarded development in a child of 7 years of age. She also suffered from adenoids, which are simply hypertrophic growths of lymphoid tissue mixed with connective tissue, this no doubt aggravated the condition and is probably present in most cases if only properly looked for as the general appearance of the patient frequently suggests it.

The high arch of the palate being generally present in children of defective mental development limits the post nasal space and so favours this condition. When

adenoids are present they depress the arch of the soft palate, block the eustachion tube causing deafness, this adding still further to the vacuous appearance , with open mouth, that this type of delicate children generally present. The deafness and tendency to catarrh being much worse in damp weather makes them very liable to attacks of bronchitis and tuberculosis which generally carries them off before they reach adult life. It appears likely from parallel cases that the ventilation of the accessory sinus and the oxygenation of the blood are interfered with; the lymph circulation at the same time is impeded or altered. The nutrition of the body is interfered with by the effects of direct pressure producing that apathetic condition which is often present in adenoids.

Gordon. (Therapeutic Gazette, Dec.15. 1907) reports that he has obtained definite improvement in cases of idiopathic epilepsy associated with defective metabolic processes on administering thyroid preparation the patient becomes brighter and the fits are greatly reduced in severity and number.

This by no means exhausts the list of cases in which thyroid gland may with advantage be given, but they give ~~give~~ those in which more especially I have had good results. In parenchymatous goitre I have had partial success.

Thyroid extract has also been given in delayed union of bones, osteomalacia, rickets, rheumatoid arthritis and delayed onset of puberty which accompanies delay of growth. It has also been tried in paralysis agitans, progressive muscular atrophy and in certain psych~~o~~sis especially those associated with disturbed thyroid function.